

Jan please

116997

Access DB# _____

SEARCH REQUEST FORM

Scientific and Technical Information Center

Requester's Full Name: S. Kumar Examiner #: 69594 Date: 3/16/04
Art Unit: 1621 Phone Number 301 571 2720 Serial Number: 10 098,192
Mail Box and Bldg/Room Location: REM 5D61 Results Format Preferred (circle) PAPER DISK E-MAIL
5C18

If more than one search is submitted, please prioritize searches in order of need. mg

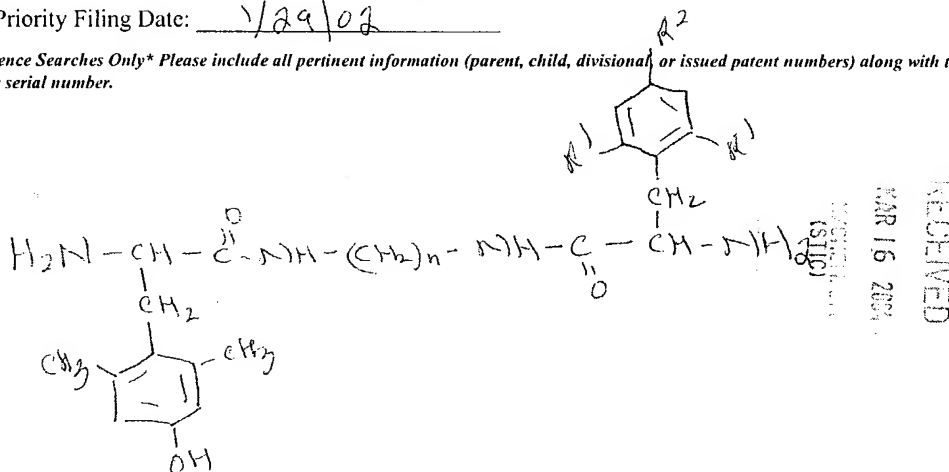
Please provide a detailed statement of the search topic, and describe as specifically as possible the subject matter to be searched. Include the elected species or structures, keywords, synonyms, acronyms, and registry numbers, and combine with the concept or utility of the invention. Define any terms that may have a special meaning. Give examples or relevant citations, authors, etc, if known. Please attach a copy of the cover sheet, pertinent claims, and abstract.

Title of Invention: Opioid derivatives

Inventors (please provide full names): Yoshio Okada et al

Earliest Priority Filing Date: 1/29/02

For Sequence Searches Only Please include all pertinent information (parent, child, divisional or issued patent numbers) along with the appropriate serial number.



R¹ is H, CH₃

R² is H, OH

n is 1 to 8

provided that R¹ is H when R² is H

STAFF USE ONLY

Searcher: Jan

Searcher Phone #: 27504

Searcher Location: _____

Date Searcher Picked Up: 3/16

Date Completed: 3/16

Searcher Prep & Review Time: _____

Clerical Prep Time: 10

Online Time: + 20

Type of Search

NA Sequence (#) _____

AA Sequence (#) _____

Structure (#) ✓

Bibliographic _____

Litigation _____

Fulltext _____

Patent Family _____

Other _____

Vendors and cost where applicable

STN ✓

Dialog _____

Questel/Orbit _____

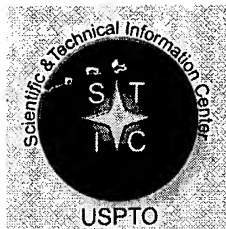
Dr.Link _____

Lexis/Nexis _____

Sequence Systems _____

WWW/Internet _____

Other (specify) _____



STIC Search Report

Biotech-Chem Library

STIC Database Tracking Number: 116997

TO: Shailendra Kumar
Location: 5d61 / 5c18
Tuesday, March 16, 2004
Art Unit: 1621
Phone: 272-0640
Serial Number: 10 / 058192

From: Jan Delaval
Location: Biotech-Chem Library
Rem 1A51
Phone: 272-2504
jan.delaval@uspto.gov

Search Notes

=> fil reg

FILE 'REGISTRY' ENTERED AT 16:06:40 ON 16 MAR 2004

USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.

PLEASE SEE "HELP USAGETERMS" FOR DETAILS.

COPYRIGHT (C) 2004 American Chemical Society (ACS)

Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 15 MAR 2004 HIGHEST RN 663595-21-9

DICTIONARY FILE UPDATES: 15 MAR 2004 HIGHEST RN 663595-21-9

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 6, 2004

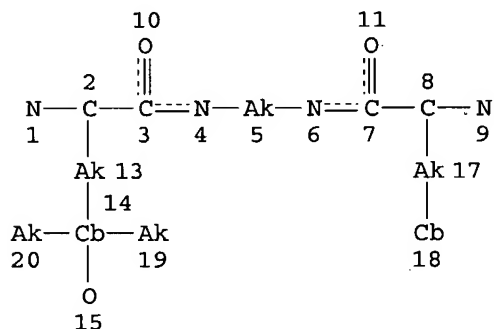
Please note that search-term pricing does apply when conducting SmartSELECT searches.

Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
<http://www.cas.org/ONLINE/DBSS/registryss.html>

=> d sta que 125

L3 STR



NODE ATTRIBUTES:

DEFAULT MLEVEL IS ATOM

DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:

RING(S) ARE ISOLATED OR EMBEDDED

NUMBER OF NODES IS 18

STEREO ATTRIBUTES: NONE

L21 SCR 1569

L24 18 SEA FILE=REGISTRY SSS FUL L3 AND L21

L25 16 SEA FILE=REGISTRY ABB=ON PLU=ON L24 NOT (156892-58-9 OR 156893-23-1)

=> d his

(FILE 'HOME' ENTERED AT 15:50:27 ON 16 MAR 2004)

SET COST OFF

FILE 'REGISTRY' ENTERED AT 15:50:38 ON 16 MAR 2004

L1 STR

L2 0 S L1

L3 STR L1
L4 0 S L3
L5 STR L1
L6 0 S L5 CSS
L7 STR L5
L8 0 S L7
L9 STR L7
L10 STR L9
L11 0 S L10 CSS
L12 SCR 2127 OR 2043
L13 0 S L10 NOT L12 CSS SAM
L14 STR L10
L15 0 S L14 CSS
L16 0 S L14 NOT L12 CSS SAM
L17 SCR 2039 OR 2127 OR 2050 OR 2049 OR 2048 OR 2053 OR 2052 OR 205
L18 0 S L14 NOT L17 CSS SAM
L19 STR L14
L20 0 S L19 CSS SAM
L21 SCR 1569
L22 0 S L3 AND L21 CSS SAM
L23 0 S L3 AND L21 SAM
L24 18 S L3 AND L21 FUL
SAV L24 KUMAR058/A
L25 16 S L24 NOT (156892-58-9 OR 156893-23-1)
L26 2 S L24 NOT L25

FILE 'HCAOLD' ENTERED AT 16:05:19 ON 16 MAR 2004

L27 0 S L25
L28 0 S L26

FILE 'HCAPLUS' ENTERED AT 16:05:22 ON 16 MAR 2004

L29 4 S L25
L30 1 S L26
L31 4 S L29,L30
L32 3 S L31 AND (OKADA Y? OR TSUDA Y? OR YOKOI T? OR BRYANT S? OR LAZ
L33 1 S L31 AND TEIKOKU?/PA,CS
L34 4 S L31-L33

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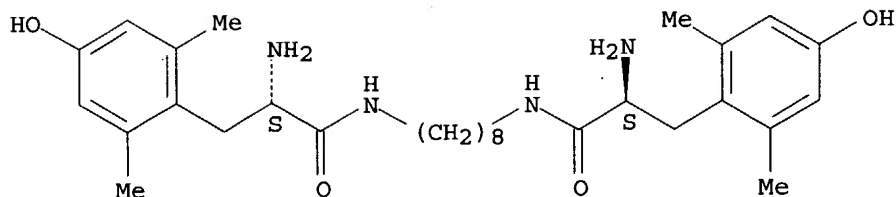
L35 3 S L25 OR L26

FILE 'REGISTRY' ENTERED AT 16:06:40 ON 16 MAR 2004

=> d ide can tot l25

L25 ANSWER 1 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 649757-31-3 REGISTRY
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α -amino-4-hydroxy-2,6-
dimethyl-, dihydrochloride, (α S, α 'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H46 N4 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (573703-41-0)

Absolute stereochemistry.



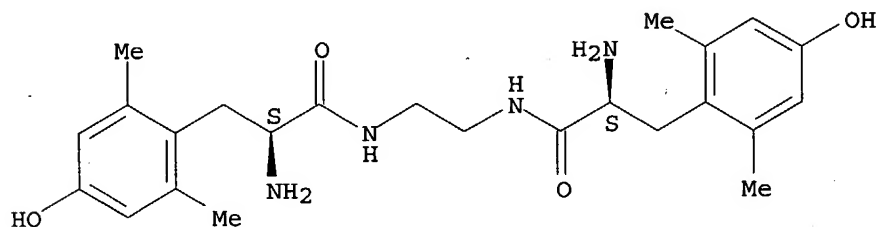
● 2 HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:128650

L25 ANSWER 2 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 649757-28-8 REGISTRY
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS
CRN (573703-38-5)

Absolute stereochemistry.



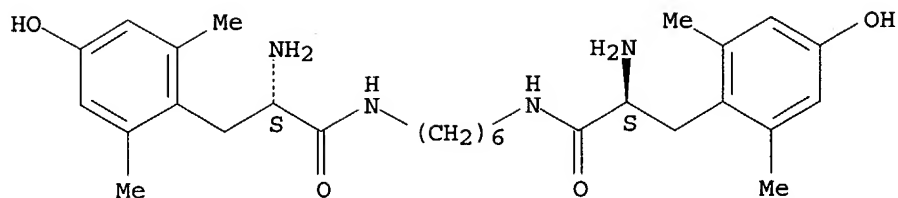
● 2 HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:128650

L25 ANSWER 3 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 577977-70-9 REGISTRY
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H42 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



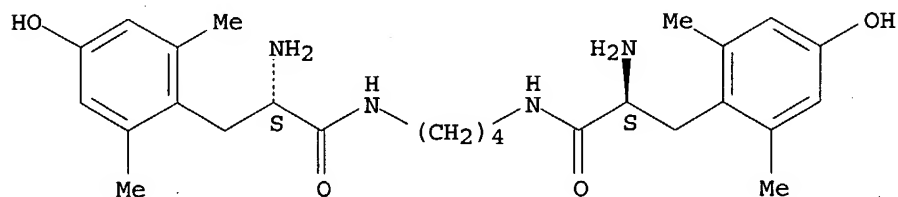
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1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 4 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 577977-67-4 REGISTRY
CN Benzenepropanamide, N,N'-1,4-butanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, ($\alpha S, \alpha' S$)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C26 H38 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



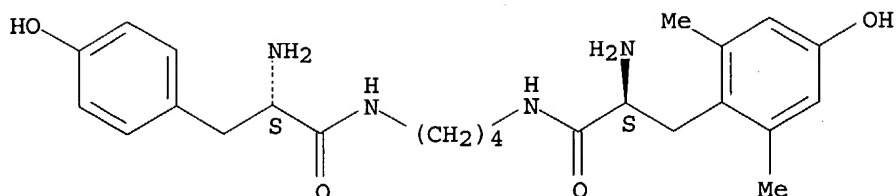
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 5 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 577977-65-2 REGISTRY
CN Benzenepropanamide, α -amino-N-[4-[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, (αS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



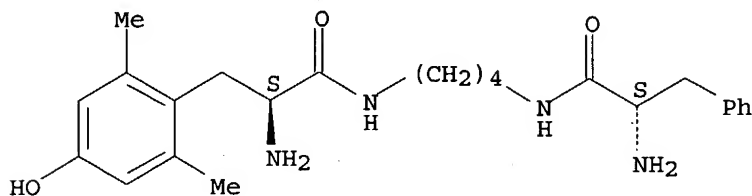
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1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 6 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 577977-61-8 REGISTRY
CN Benzenepropanamide, α -amino-N-[4-[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, (α S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O3
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

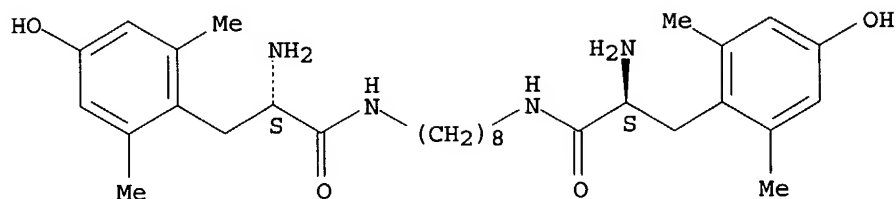
REFERENCE 1: 139:173182

L25 ANSWER 7 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-42-1 REGISTRY
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, (α S, α 'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C30 H46 N4 O4 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

CRN 573703-41-0
CMF C30 H46 N4 O4

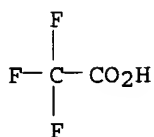
Absolute stereochemistry.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



2 REFERENCES IN FILE CA (1907 TO DATE)

2 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

REFERENCE 2: 139:164977

L25 ANSWER 8 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN

RN 573703-41-0 REGISTRY

CN Benzenepropanamide, N,N'-1,8-octanediylbis[alpha-amino-4-hydroxy-2,6-dimethyl-, (alphaS, alpha'S)- (9CI) (CA INDEX NAME)

FS STEREOSEARCH

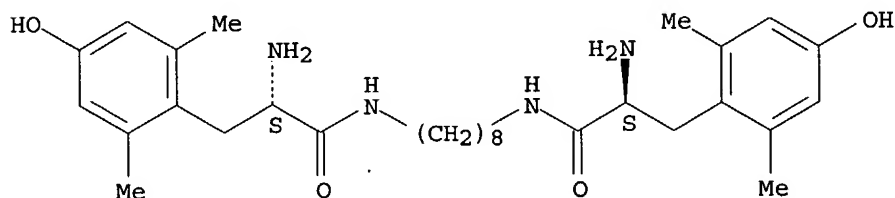
MF C30 H46 N4 O4

CI COM

SR CA

LC STN Files: CA, CAPLUS

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)

1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 9 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN

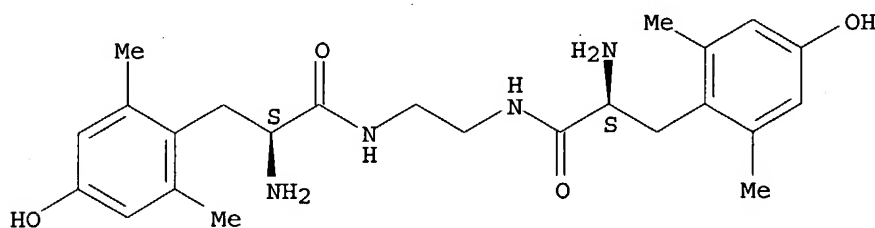
RN 573703-39-6 REGISTRY

CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, (α S, α 'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4 . 2 C2 H F3 O2
SR CA
LC STN Files: CA, CAPLUS, USPATFULL

CM 1

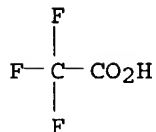
CRN 573703-38-5
CMF C24 H34 N4 O4

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

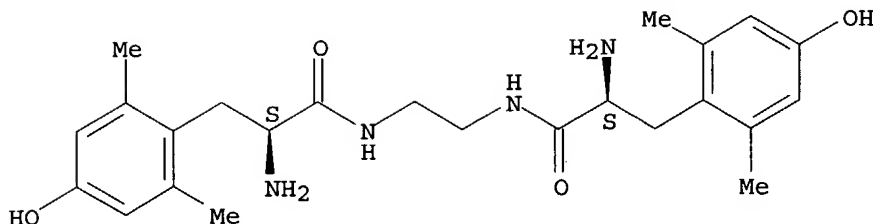


1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:164977

L25 ANSWER 10 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-38-5 REGISTRY
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, (α S, α 'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4
CI COM
SR CA
LC STN Files: CA, CAPLUS

Absolute stereochemistry.



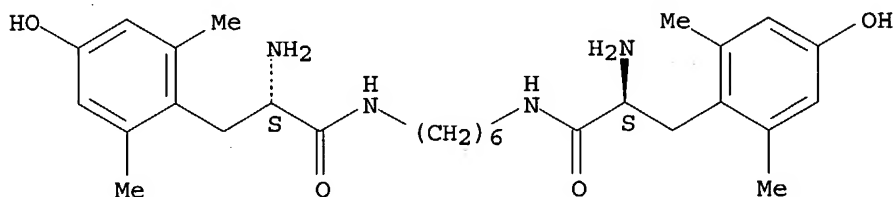
PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

1 REFERENCES IN FILE CA (1907 TO DATE)
1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 139:173182

L25 ANSWER 11 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-36-3 REGISTRY
CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C28 H42 N4 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (577977-70-9)

Absolute stereochemistry.



●2 HCl

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

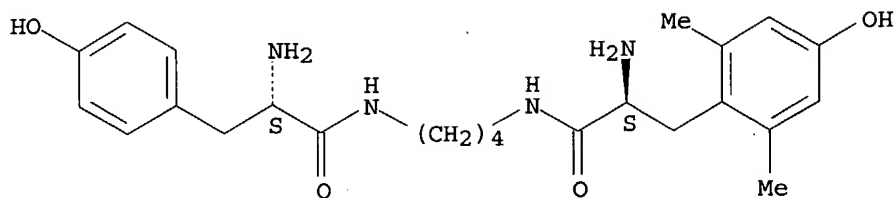
REFERENCE 1: 140:128650

REFERENCE 2: 139:173182

REFERENCE 3: 139:164977

L25 ANSWER 12 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-34-1 REGISTRY
CN Benzenepropanamide, α-amino-N-[4-[[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS)- (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O4 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (577977-65-2)

Absolute stereochemistry.



● 2 HCl

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

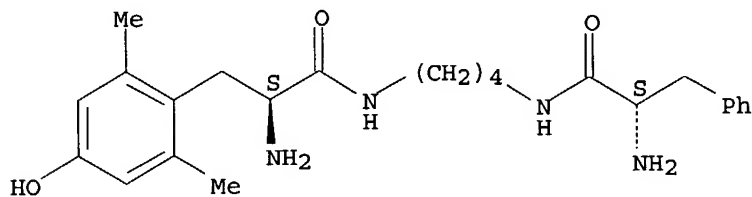
REFERENCE 1: 140:128650

REFERENCE 2: 139:173182

REFERENCE 3: 139:164977

L25 ANSWER 13 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-31-8 REGISTRY
CN Benzenepropanamide, α -amino-N-[4-[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S) - (9CI) (CA INDEX NAME)
FS STEREOSEARCH
MF C24 H34 N4 O3 . 2 Cl H
SR CA
LC STN Files: CA, CAPLUS, USPATFULL
CRN (577977-61-8)

Absolute stereochemistry.



● 2 HCl

3 REFERENCES IN FILE CA (1907 TO DATE)
3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 140:128650

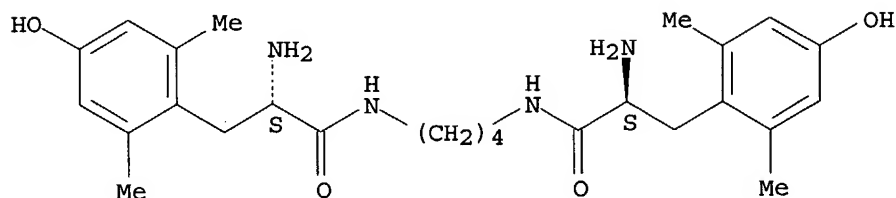
REFERENCE 2: 139:173182

REFERENCE 3: 139:164977

L25 ANSWER 14 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
RN 573703-27-2 REGISTRY
CN Benzenepropanamide, N,N'-1,4-butanediylbis[α -amino-4-hydroxy-2,6-

dimethyl-, dihydrochloride, (α S, α' S)- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C26 H38 N4 O4 . 2 Cl H
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL
 CRN (577977-67-4)

Absolute stereochemistry.



● 2 HCl

3 REFERENCES IN FILE CA (1907 TO DATE)
 3 REFERENCES IN FILE CAPLUS (1907 TO DATE)

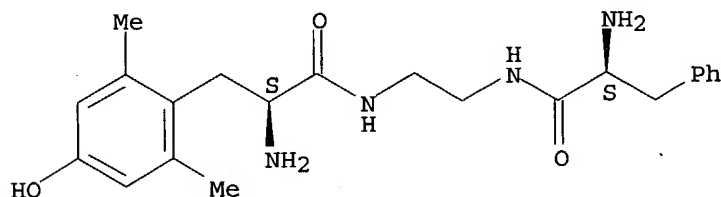
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REFERENCE 2: 139:173182

REFERENCE 3: 139:164977

L25 ANSWER 15 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 156893-25-3 REGISTRY
 CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C22 H30 N4 O3
 CI COM
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

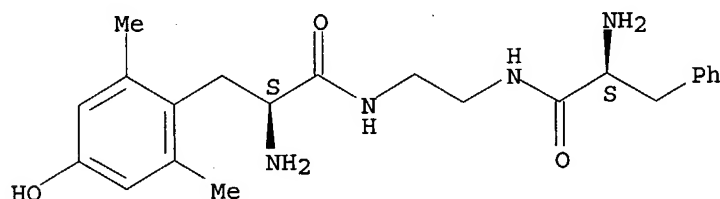
1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 121:134808

L25 ANSWER 16 OF 16 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 156892-66-9 REGISTRY

CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C22 H30 N4 O3 . 2 Cl H
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL
 CRN (156893-25-3)

Absolute stereochemistry.



● 2 HCl

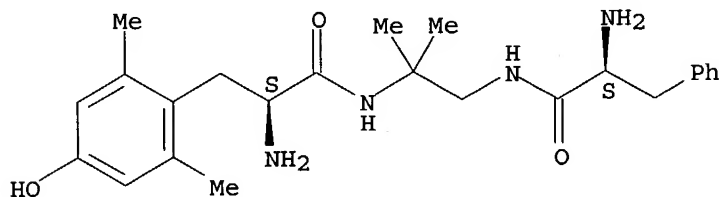
1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 121:134808

=> d ide can tot 126

L26 ANSWER 1 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN
 RN 156893-23-1 REGISTRY
 CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C24 H34 N4 O3
 CI COM
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL

Absolute stereochemistry.



PROPERTY DATA AVAILABLE IN THE 'PROP' FORMAT

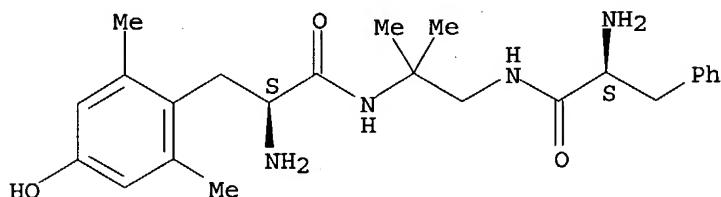
1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 121:134808

L26 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2004 ACS on STN

RN 156892-58-9 REGISTRY
 CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)
 FS STEREOSEARCH
 MF C24 H34 N4 O3 . 2 Cl H
 SR CA
 LC STN Files: CA, CAPLUS, USPATFULL
 CRN (156893-23-1)

Absolute stereochemistry.



● 2 HCl

1 REFERENCES IN FILE CA (1907 TO DATE)
 1 REFERENCES IN FILE CAPLUS (1907 TO DATE)

REFERENCE 1: 121:134808

=> fil uspatall
 FILE 'USPATFULL' ENTERED AT 16:07:00 ON 16 MAR 2004
 CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

FILE 'USPAT2' ENTERED AT 16:07:00 ON 16 MAR 2004
 CA INDEXING COPYRIGHT (C) 2004 AMERICAN CHEMICAL SOCIETY (ACS)

=> d l35 bib abs hitstr tot

L35 ANSWER 1 OF 3 USPATFULL on STN
 AN 2003:244888 USPATFULL
 TI Opioid derivative
 IN Okada, Yoshio, Akashi-shi, JAPAN
 Tsuda, Yuko, Akashi-shi, JAPAN
 Yokoi, Toshio, Akashi-shi, JAPAN
 Bryant, Sharon D., Chapel Hill, NC, UNITED STATES
 Lazarus, Lawrence H., Durham, NC, UNITED STATES
 PI US 2003171302 A1 20030911
 AI US 2002-58192 A1 20020129 (10)
 DT Utility
 FS APPLICATION
 LREP BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
 CLMN Number of Claims: 7
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 966
 CAS INDEXING IS AVAILABLE FOR THIS PATENT.
 AB 1. A peptide derivative represented by the following formula (1) or a salt thereof; ##STR1##

, wherein R.sup.1 is hydrogen atom or methyl group, R.sup.2 is hydrogen atom or hydroxy group and n is an integer of 1-8, provided that R.sup.1

is hydrogen atom when R.sup.2 is hydrogen atom, which has specific and high binding affinity with the μ -opioid receptor.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

IT 573703-27-2P 573703-31-8P 573703-34-1P

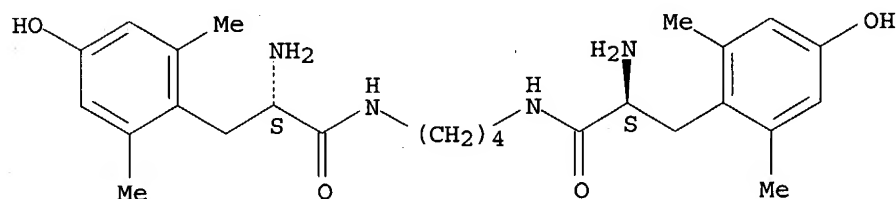
573703-36-3P 573703-39-6P 573703-42-1P

(preparation of tyrosine alkanediamide derivs. having μ -opioid binding affinity)

RN 573703-27-2 USPATFULL

CN Benzenepropanamide, N,N'-1,4-butanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S, α 'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

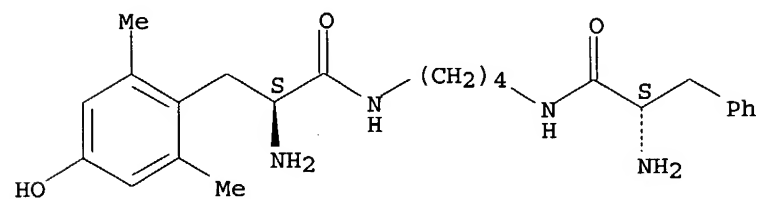


● 2 HCl

RN 573703-31-8 USPATFULL

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

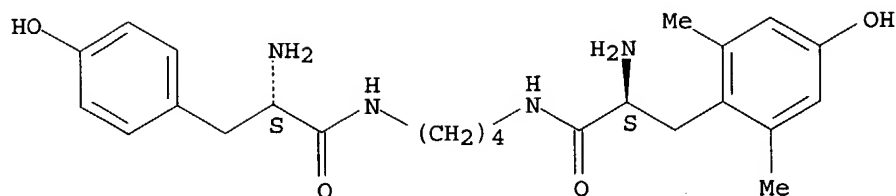


● 2 HCl

RN 573703-34-1 USPATFULL

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

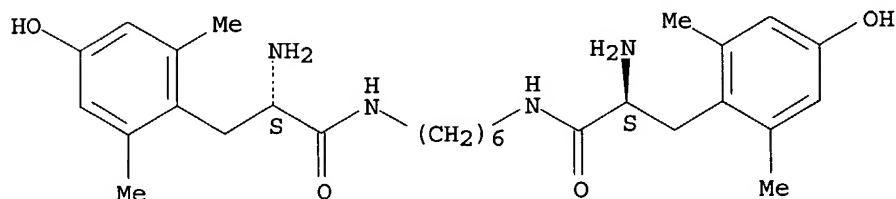


● 2 HCl

RN 573703-36-3 USPATFULL

CN Benzenepropanamide, N,N'-1,6-hexanediylbis[alpha-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (alphaS, alpha'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

RN 573703-39-6 USPATFULL

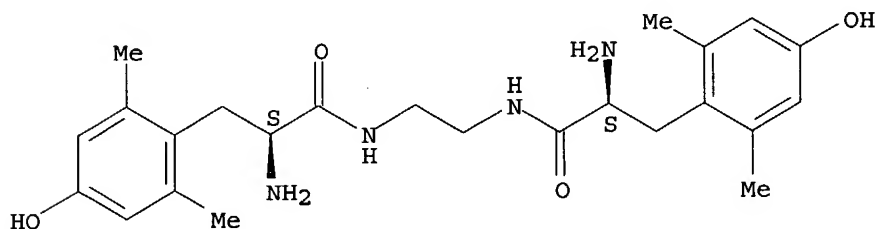
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[alpha-amino-4-hydroxy-2,6-dimethyl-, (alphaS, alpha'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 573703-38-5

CMF C24 H34 N4 O4

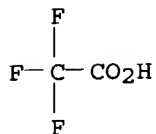
Absolute stereochemistry.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 573703-42-1 USPATFULL

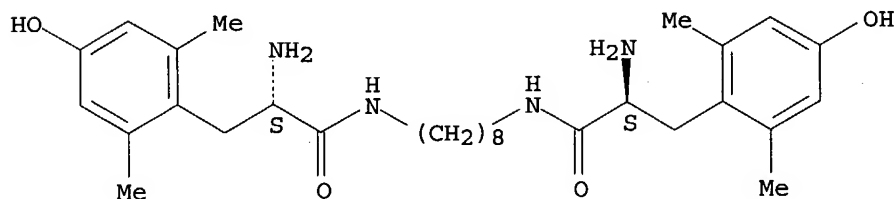
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI)
(CA INDEX NAME)

CM 1

CRN 573703-41-0

CMF C30 H46 N4 O4

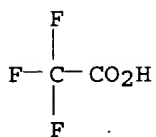
Absolute stereochemistry.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



L35 ANSWER 2 OF 3 USPATFULL on STN

AN 94:99903 USPATFULL

TI Substituted tyrosyl diamide compounds

IN Hansen, Jr., Donald W., Skokie, IL, United States

Chandrakumar, Nizal S., Vernon Hills, IL, United States

Peterson, Karen B., Vernon Hills, IL, United States

Tsymbalov, Sofya, Des Plaines, IL, United States

Husa, Robert K., Gurnee, IL, United States

PA G. D. Searle & Co., Chicago, IL, United States (U.S. corporation)

PI US 5364850 19941115

AI US 1993-125897 19930924 (8)

RLI Division of Ser. No. US 1992-886276, filed on 20 May 1992, now patented,
Pat. No. US 5272175

DT Utility

FS Granted

EXNAM Primary Examiner: Raymond, Richard L.

LREP Hastreiter, Roberta L., Williams, Roger A.

CLMN Number of Claims: 22

ECL Exemplary Claim: 1

DRWN No Drawings

LN.CNT 2287

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides substituted tyrosyl diamide compounds of general Formula I: ##STR1## and the pharmaceutically-acceptable salts thereof, which are useful for inducing analgesia in animals, pharmaceutical compositions comprising a pharmaceutically-acceptable carrier and a compound of Formula I, and a method for inducing analgesia in an animal in need thereof comprising administering a therapeutically-effective amount of a compound of Formula I to the animal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

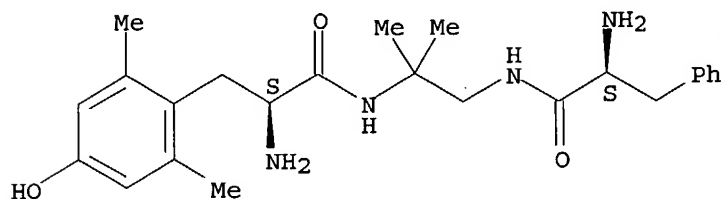
IT 156892-58-9P 156892-66-9P 156893-23-1P
156893-25-3P

(preparation of, as analgesic)

RN 156892-58-9 USPATFULL

CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

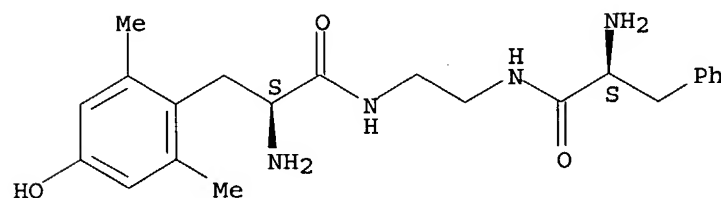


● 2 HCl

RN 156892-66-9 USPATFULL

CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

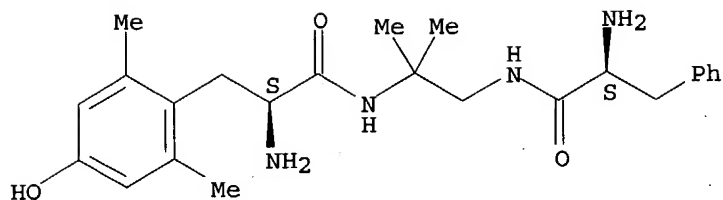


● 2 HCl

RN 156893-23-1 USPATFULL

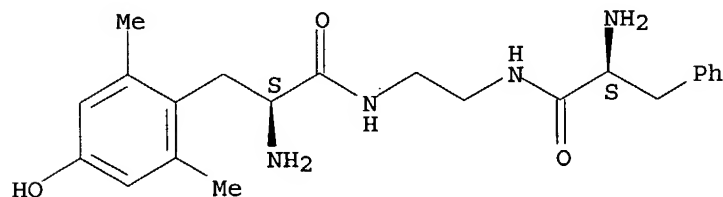
CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 156893-25-3 USPATFULL
 CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI)
 (CA INDEX NAME)

Absolute stereochemistry.



L35 ANSWER 3 OF 3 USPATFULL on STN
 AN 93:107046 USPATFULL
 TI Substituted tyrosyl diamide compounds
 IN Hansen, Jr., Donald W., Skokie, IL, United States
 Chandrakumar, Nizal S., Vernon Hills, IL, United States
 Peterson, Karen B., Vernon Hills, IL, United States
 Tsymbalov, Sofya, Des Plaines, IL, United States
 Husa, Robert K., Vernon Hills, IL, United States
 PA G. D. Searle & Co., Chicago, IL, United States (U.S. corporation)
 PI US 5272175 19931221
 AI US 1992-886276 19920520 (7)
 DT Utility
 FS Granted
 EXNAM Primary Examiner: Raymond, Richard L.
 LREP Hastreiter, Roberta L., Williams, Roger A.
 CLMN Number of Claims: 30
 ECL Exemplary Claim: 1
 DRWN No Drawings
 LN.CNT 2547

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides substituted tyrosyl diamide compounds of general Formula I: ##STR1## and the pharmaceutically-acceptable salts thereof, which are useful for inducing analgesia in animals, pharmaceutical compositions comprising a pharmaceutically-acceptable carrier and a compound of Formula I, and a method for inducing analgesia in an animal in need thereof comprising administering a therapeutically-effective amount of a compound of Formula I to the animal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

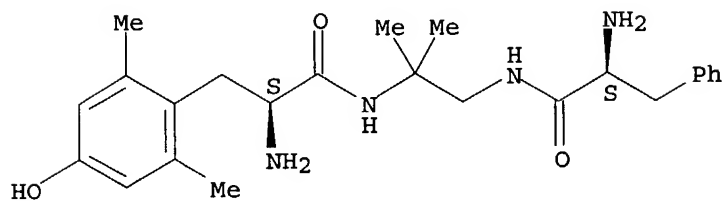
IT 156892-58-9P 156892-66-9P 156893-23-1P
 156893-25-3P

(preparation of, as analgesic)

RN 156892-58-9 USPATFULL

CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

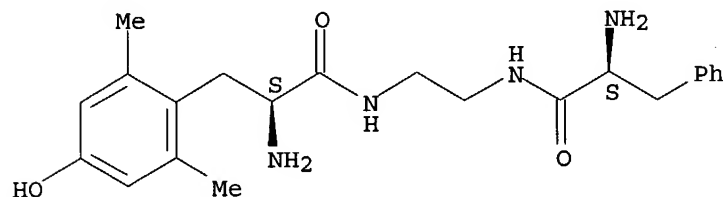


● 2 HCl

RN 156892-66-9 USPATFULL

CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

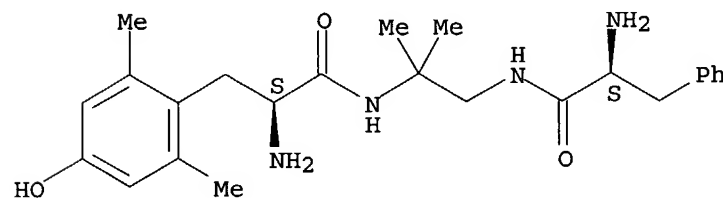


● 2 HCl

RN 156893-23-1 USPATFULL

CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

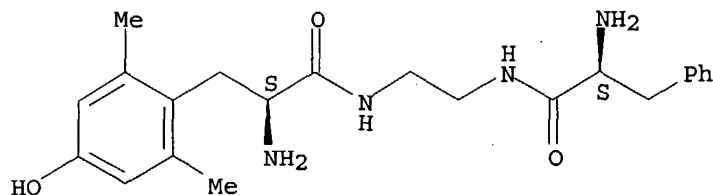
Absolute stereochemistry.



RN 156893-25-3 USPATFULL

CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 16:07:14 ON 16 MAR 2004

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FILE COVERS 1907 - 16 Mar 2004 VOL 140 ISS 12

FILE LAST UPDATED: 15 Mar 2004 (20040315/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

=> d all hitstr tot 134

L34 ANSWER 1 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:610409 HCAPLUS

DN 139:164977

ED Entered STN: 08 Aug 2003

TI Preparation of tyrosine alkanediamide derivs. having μ -opioid binding affinity

IN Okada, Yoshio; Tsuda, Yuko; Yokoi, Toshio;

Bryant, Sharon D.; Lazarus, Lawrence H.

PA Teikoku Seiyaku Co., Ltd., Japan

SO PCT Int. Appl., 50 pp.

CODEN: PIXXD2

DT Patent

LA English

IC ICM C07C237-20

ICS A61K031-165; A61P025-04; A61P043-00

CC 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 1, 2

FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003064375	A1	20030807	WO 2003-JP516	20030122
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL,				

PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA,
 UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
 RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG,
 CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC,
 NL, PT, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW,
 ML, MR, NE, SN, TD, TG

US 2003171302 A1 20030911 US 2002-58192 20020129

PRAI US 2002-58192 A 20020129

OS MARPAT 139:164977

AB Peptide derivs. 2,6,4-Me₂(HO)C₆H₂CH₂CH(NH₂)CONH(CH₂)_nNHCOCH(NH₂)CH₂C₆H₂R₁₂
 R₂-2,6,4 (R₁ = H or Me; R₂ = H or OH; n = 1-8, provided that R₁ is H when
 R₂ is H), having specific and high binding affinity with the μ -opioid
 receptor, were prepared Thus, 1,4-bis(Dmt-amino)butane.2HCl and
 1,6-bis(Dmt-amino)hexane.2HCl (Dmt = 2,6-dimethyl-L-tyrosine residue) were
 prepared and shown to have δ - and μ -receptor affinities of $133 \pm$
 $18 \text{ nM}/0.38 \pm 0.02 \text{ nM}$ and $53.4 \pm 14.8 \text{ nM}/0.041 \pm 0.003 \text{ nM}$, resp.,
 and to have analgesic activity via the μ -opioid receptor.

ST tyrosine alkanediamide prepn opioid binding analgesic

IT Analgesics

Nerve, disease

Pain

(preparation of tyrosine alkanediamide derivs. having μ -opioid binding
 affinity)

IT Opioids

Peptides, preparation

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(preparation of tyrosine alkanediamide derivs. having μ -opioid binding
 affinity)

IT Amino acids, reactions

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of tyrosine alkanediamide derivs. having μ -opioid binding
 affinity)

IT Opioid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)
 (μ -opioid; preparation of tyrosine alkanediamide derivs. having
 μ -opioid binding affinity)

IT 573703-27-2P 573703-31-8P 573703-34-1P

573703-36-3P 573703-39-6P 573703-42-1P

573703-44-3P 573703-46-5P 573703-49-8P 573703-52-3P 574705-94-5P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(preparation of tyrosine alkanediamide derivs. having μ -opioid binding
 affinity)

IT 107-15-3, 1 2 Diaminoethane, reactions 110-60-1, 1 4 Diaminobutane

124-09-4, 1 6 Diaminohexane, reactions 373-44-4, 1 8 Diaminooctane

3978-80-1 13734-34-4 35661-40-6 68076-36-8 126312-63-8

147688-40-2

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of tyrosine alkanediamide derivs. having μ -opioid binding
 affinity)

IT 81649-48-1P 99953-00-1P 573703-26-1P 573703-28-3P 573703-30-7P

573703-32-9P 573703-33-0P 573703-35-2P 573703-37-4P 573703-40-9P

573703-43-2P 573703-45-4P 573703-47-6P 573703-50-1P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
 (Reactant or reagent)

(preparation of tyrosine alkanediamide derivs. having μ -opioid binding
 affinity)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

(1) Fukumizu, J; 120th Annual Conference of the Pharmaceutical Society of Japan

in Gifu 2000

- (2) Fukumizu, J; Nippon Yakugakkai Dai 120 Nenkaishu, Gifu 2000, P129
 (3) G D Searle & Co; US 5272175 A 1993 HCAPLUS
 (4) Okada, Y; Tetrahedron 1999, V55(50), P14391 HCAPLUS
 (5) Teikoku Seiyaku Kabushiki Kaisha; JP 200269059 A 2002

IT 573703-27-2P 573703-31-8P 573703-34-1P

573703-36-3P 573703-39-6P 573703-42-1P

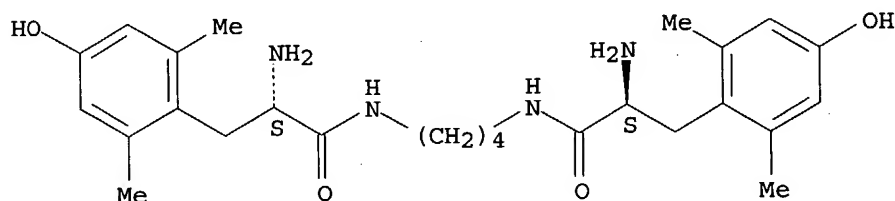
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU
 (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES
 (Uses)

(preparation of tyrosine alkanediamide derivs. having μ -opioid binding
 affinity)

RN 573703-27-2 HCAPLUS

CN Benzenepropanamide, N,N'-1,4-butanediylbis[α -amino-4-hydroxy-2,6-
 dimethyl-, dihydrochloride, (α S, α' S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

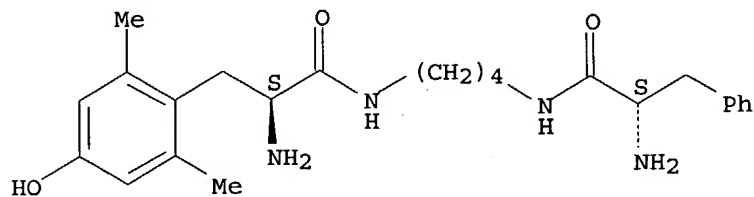


● 2 HCl

RN 573703-31-8 HCAPLUS

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-1-oxo-3-
 phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride,
 (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

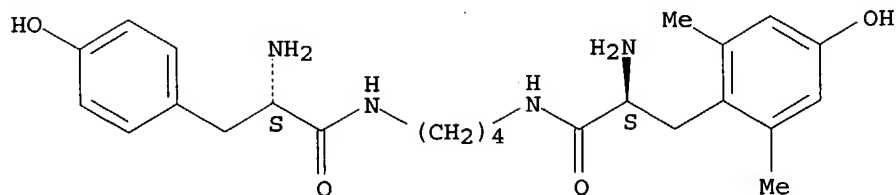


● 2 HCl

RN 573703-34-1 HCAPLUS

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-3-(4-hydroxyphenyl)-
 1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride,
 (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

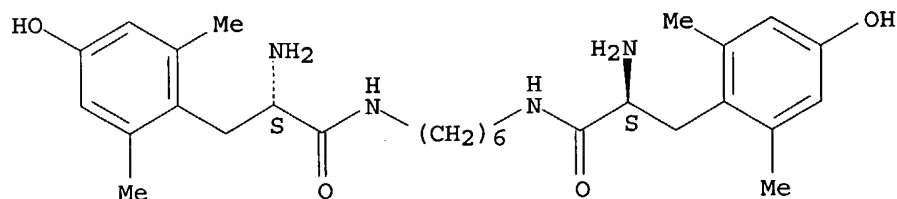


● 2 HCl

RN 573703-36-3 HCAPLUS

CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

RN 573703-39-6 HCAPLUS

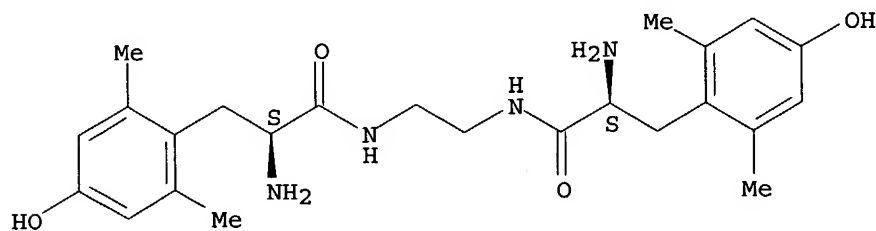
CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 573703-38-5

CMF C24 H34 N4 O4

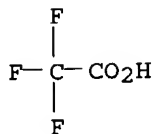
Absolute stereochemistry.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



RN 573703-42-1 HCAPLUS

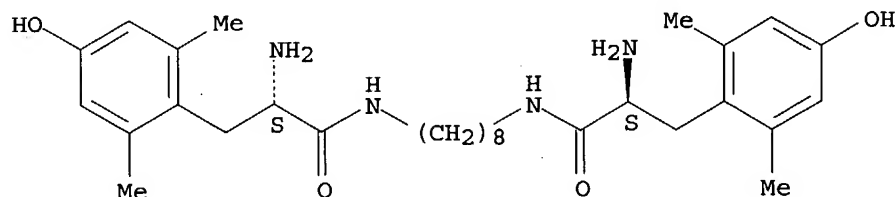
CN Benzenepropanamide, N,N'-1,8-octanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, (α S, α 'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 573703-41-0

CMF C30 H46 N4 O4

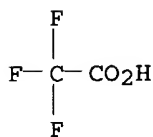
Absolute stereochemistry.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



L34 ANSWER 2 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:459812 HCAPLUS

DN 139:173182

ED Entered STN: 17 Jun 2003

TI Unique High-Affinity Synthetic μ -Opioid Receptor Agonists with Central- and Systemic-Mediated Analgesia

AU Okada, Yoshio; Tsuda, Yuko; Fujita, Yoshio; Yokoi, Toshio; Sasaki, Yusuke; Ambo, Akihiro; Konishi, Ryoji; Nagata, Mitsuhiro; Salvadori, Severo; Jinsmaa, Yunden; Bryant, Sharon D.; Lazarus, Lawrence H.

CS Faculty of Pharmaceutical Sciences, Department of Medicinal Chemistry and High Technology Research Center, Kobe Gakuin University, Nishi, Kobe, 651-2180, Japan

SO Journal of Medicinal Chemistry (2003), 46(15), 3201-3209
CODEN: JMCMAR; ISSN: 0022-2623

PB American Chemical Society

DT Journal

LA English

CC 1-3 (Pharmacology)

Section cross-reference(s): 34

AB Unique opioid mimetic substances containing identical N-terminal aromatic residues separated by an unbranched alkyl chain containing two to eight methylene

groups were developed. Regardless of the length of interposing alkyl chain, the bis-Tyr and bis-Phe compds. were inactive; however, replacement by a single Dmt (2',6'-dimethyl-L-tyrosine) residue enhanced activity by orders of magnitude. Moreover, the bis-Dmt compds. were another 10-fold more potent with an optimum intra-aromatic ring distance of about four to six methylene units. 1,4-Bis(Dmt-NH)butane had high μ -opioid receptor affinity ($K_i = 0.041$ nM) and functional μ -opioid agonist bioactivity ($IC_{50} = 5.3$ nM) with in vivo central (intracerebroventricular) and systemic (s.c.) analgesia in mice (1.5- to 2.5-fold greater than and 10-12% relative to morphine, resp.); these activities were reversed by naloxone to the same degree. It appears that the bis-Dmt compds. indiscriminately act as both message and address domains.

ST μ opioid receptor agonist analgesic

IT Analgesics

Conformation

Molecular association

Molecular modeling

NMR (nuclear magnetic resonance)

(preparation of unique high-affinity synthetic μ -opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT Opioids

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)

(μ -; preparation of unique high-affinity synthetic μ -opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT Structure-activity relationship

(μ -opioid; preparation of unique high-affinity synthetic μ -opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT Opioid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study)

(μ -opioid; preparation of unique high-affinity synthetic μ -opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT 577977-61-8 577977-65-2 577977-67-4

RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of unique high-affinity synthetic μ -opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT 573703-27-2P 573703-31-8P 573703-34-1P

573703-36-3P 573703-42-1P 573703-44-3P 573703-46-5P

573703-52-3P 577977-87-8P 577977-88-9P 577977-89-0P

RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of unique high-affinity synthetic μ -opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT 76597-36-9 81638-49-5 573703-38-5 573703-41-0

573703-48-7 577977-56-1 577977-70-9

RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of unique high-affinity synthetic μ -opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

IT 107-15-3, 1,2-Diaminoethane, reactions 124-09-4, 1,6-Diaminohexane,

reactions 373-44-4, 1,8-Diaminooctane 3978-80-1 35661-40-6

68076-36-8 99953-00-1 147688-40-2 573703-26-1

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of unique high-affinity synthetic μ -opioid receptor agonists

with central- and systemic-mediated analgesia in relation to structure)
IT 110-60-1P, 1,4-Diaminobutane 81649-48-1P 573703-28-3P 573703-30-7P
573703-32-9P 573703-33-0P 573703-35-2P 573703-37-4P 573703-40-9P
573703-43-2P 573703-45-4P 573703-47-6P 573703-51-2P 577977-81-2P
577977-86-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT
(Reactant or reagent)
(preparation of unique high-affinity synthetic μ -opioid receptor agonists
with central- and systemic-mediated analgesia in relation to structure)

RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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IT 577977-61-8 577977-65-2 577977-67-4

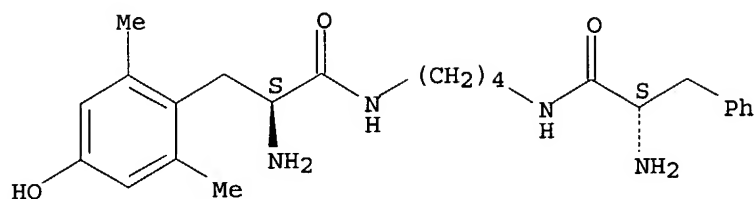
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of unique high-affinity synthetic μ -opioid receptor agonists
with central- and systemic-mediated analgesia in relation to structure)

RN 577977-61-8 HCAPLUS

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, (α S)- (9CI) (CA INDEX NAME)

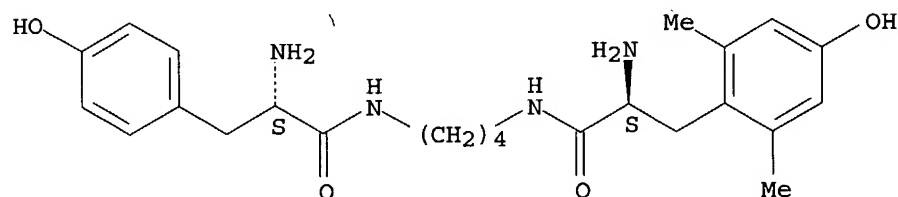
Absolute stereochemistry.



RN 577977-65-2 HCAPLUS

CN Benzenepropanamide, α-amino-N-[4-[[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, (αS)- (9CI) (CA INDEX NAME)

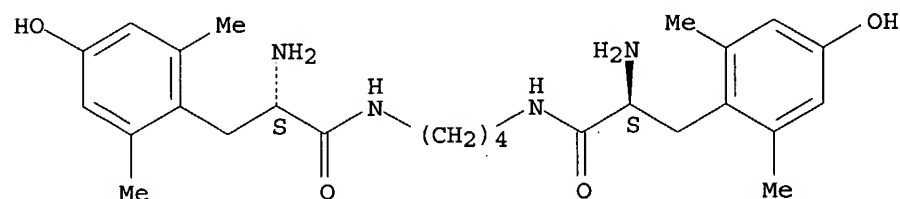
Absolute stereochemistry.



RN 577977-67-4 HCAPLUS

CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT 573703-27-2P 573703-31-8P 573703-34-1P

573703-36-3P 573703-42-1P

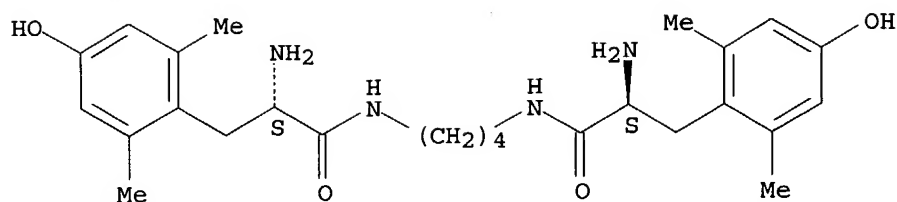
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

RN 573703-27-2 HCAPLUS

CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

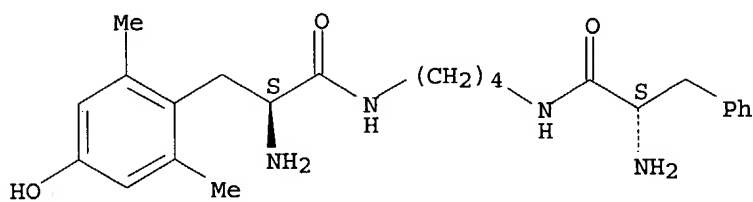


●2 HCl

RN 573703-31-8 HCAPLUS

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

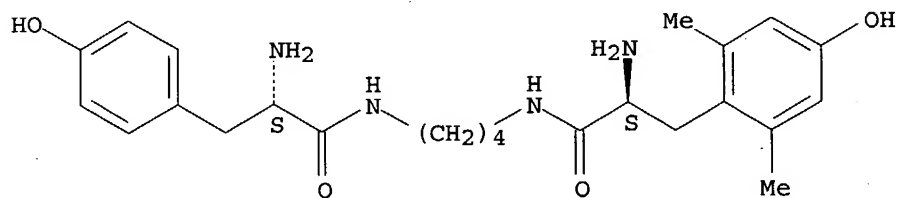


●2 HCl

RN 573703-34-1 HCAPLUS

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

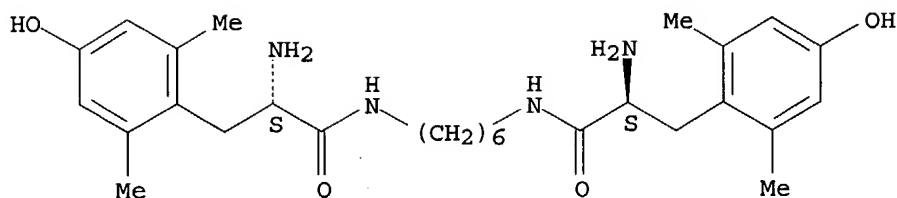


●2 HCl

RN 573703-36-3 HCAPLUS

CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S, α' S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

RN 573703-42-1 HCAPLUS

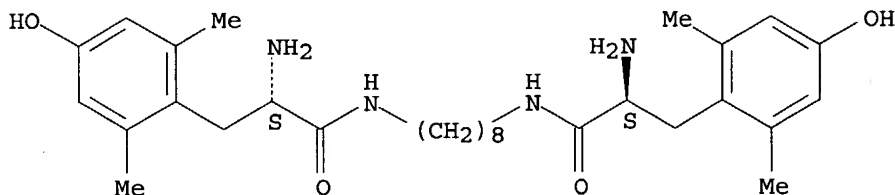
CN Benzenepropanamide, N,N'-1,8-octanediyldis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)-, bis(trifluoroacetate) (salt) (9CI) (CA INDEX NAME)

CM 1

CRN 573703-41-0

CMF C30 H46 N4 O4

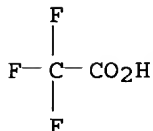
Absolute stereochemistry.



CM 2

CRN 76-05-1

CMF C2 H F3 O2



IT 573703-38-5 573703-41-0 577977-70-9

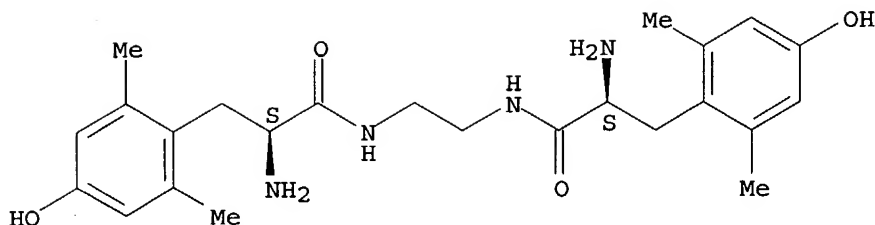
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(preparation of unique high-affinity synthetic μ-opioid receptor agonists with central- and systemic-mediated analgesia in relation to structure)

RN 573703-38-5 HCAPLUS

CN Benzenepropanamide, N,N'-1,2-ethanediyldis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)

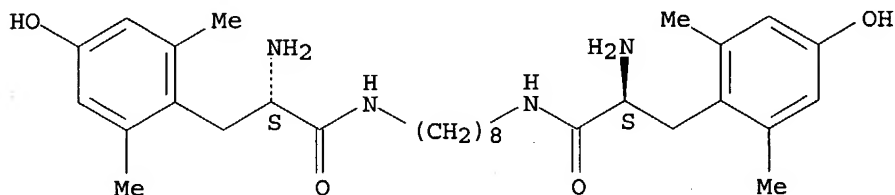
Absolute stereochemistry.



RN 573703-41-0 HCAPLUS

CN Benzenepropanamide, N,N'-1,8-octanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)

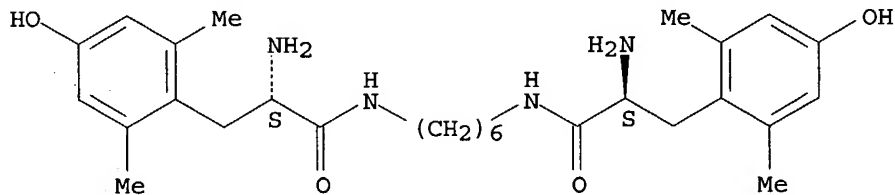
Absolute stereochemistry.



RN 577977-70-9 HCAPLUS

CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



L34 ANSWER 3 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 2003:449478 HCAPLUS

DN 140:128650

ED Entered STN: 12 Jun 2003

TI Design of opioid-mimetics: dimerization of 2', 6'-dimethyl-L-tyrosine

AU Tsuda, Yuko; Fujita, Yoshio; Miyazaki, Anna; Shiotani, Kimitaka;

Fujisawa, Yutaka; Yokoi, Toshio; Li, Tingyou; Ambo, Akihiro;

Sasaki, Yusuke; Bryant, Sharon D.; Lazarus, Lawrence H.

; Okada, Yoshio

CS Faculty of Pharmaceutical Sciences, Kobe Gakuin University, Nishi-ku, Kobe, 651-2180, Japan

SO Peptide Science (2003), Volume Date 2002, 39th, 105-108

CODEN: PSCIFQ; ISSN: 1344-7661

PB Japanese Peptide Society

DT Journal

LA English

CC 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 1, 2, 22

AB In order to obtain the potent and selective μ -agonists, dimerization of 2',6'-dimethyl-L-tyrosine (Dmt) was carried out. As a spacer, alkyldiamine and a pyrazinone ring (Pyr) platform extended with amino

groups were used. Opioid-mimetics Dmt-NH-(CH₂)₄-NH-Tyr and Dmt-NH-(Orn-Orn)-Pyr-NH-Dmt exhibited high μ -binding affinity, selectivity and fairly potent μ -agonism in vitro. Furthermore, Dmt-NH-(Orn-Orn)-Pyr-NH-Dmt had more potent antinociceptive activity than morphine after i.c.v. administration.

- ST opioid mimetic pseudopeptide prepn antinociceptive conformation NMR simulation modeling; peptidomimetic opioid receptor binding structure activity analgesic; tyrosine dimethyl dimerization alkyl diamine pyrazinone tertiary structure CD
- IT Structure-activity relationship
(analgesic; preparation of opioid-mimetics by dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)
- IT Conformation
(preparation and conformation by NMR and simulation and modeling of opioid-mimetics with antinociceptive activity)
- IT Tertiary structure
(preparation and tertiary structure by simulation and modeling and CD of opioid-mimetics with antinociceptive activity)
- IT Dimerization
(preparation of opioid-mimetics by dimerization of dimethyltyrosine using alkyl diamine or pyrazinone ring with amino groups as spacer)
- IT Analgesics
Pain
(preparation of opioid-mimetics with antinociceptive activity by dimerization of dimethyltyrosine)
- IT Peptidomimetics
(preparation of peptidomimetics, analgesic and opioid receptor-binding structure-activity relationship)
- IT Simulation and Modeling, physicochemical
(preparation, conformation and tertiary structure by NMR, simulation and modeling, and CD of opioid-mimetics with antinociceptive activity)
- IT Peptides, preparation
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(pseudopeptides; preparation of pseudopeptides by dimerization of dimethyltyrosine using alkyl diamine or pyrazinone ring with amino groups as spacer)
- IT Opioids
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(δ -; preparation of opioid-mimetics by dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)
- IT Structure-activity relationship
(δ -opioid receptor-binding; preparation of opioid-mimetics by dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)
- IT Opioid receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(δ -opioid; preparation of opioid-mimetics by dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)
- IT Opioids
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(μ -; preparation of opioid-mimetics by dimerization of dimethyltyrosine and their μ -opioid receptor-binding structure-activity relationship)
- IT Structure-activity relationship
(μ -opioid receptor-binding; preparation of opioid-mimetics by

dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT Opioid receptors

RL: BSU (Biological study, unclassified); BIOL (Biological study) (μ -opioid; preparation of opioid-mimetics by dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT 110449-60-0P 234450-16-9P 403476-93-7P 489473-59-8P 489473-60-1P
489473-61-2P 489473-62-3P 489473-63-4P 489473-64-5P
573703-31-8P 573703-34-1P 573703-36-3P
573703-44-3P 649757-27-7P 649757-28-8P 649757-29-9P
649757-30-2P 649757-31-3P

RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of opioid-mimetics by dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT 234450-03-4 649757-32-4 649757-33-5 649757-34-6

RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of opioid-mimetics by dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

IT 573703-27-2P

RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of opioid-mimetics by dimerization of dimethyltyrosine, their conformation, analgesic and opioid receptor-binding structure-activity relationship)

RE.CNT 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD

RE

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- (2) Lazarus, L; J Biol Chem 1989, V264, P354 HCAPLUS
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IT 573703-31-8P 573703-34-1P 573703-36-3P
649757-28-8P 649757-31-3P

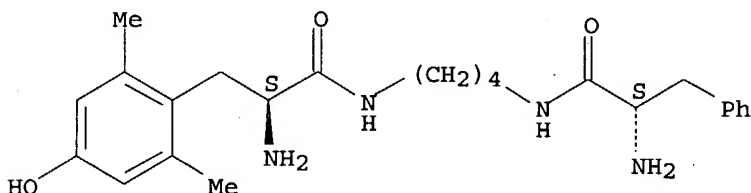
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of opioid-mimetics by dimerization of dimethyltyrosine, their analgesic and opioid receptor-binding structure-activity relationship)

RN 573703-31-8 HCAPLUS

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-1-oxo-3-phenylpropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

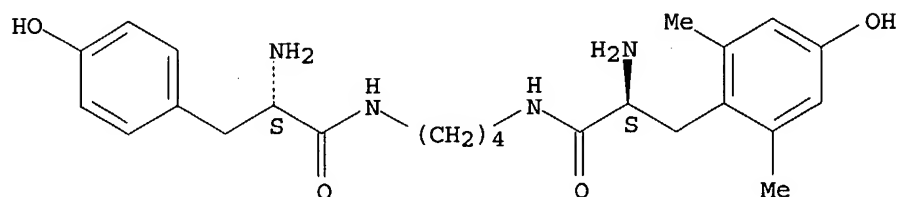


● 2 HCl

RN 573703-34-1 HCAPLUS

CN Benzenepropanamide, α -amino-N-[4-[[[(2S)-2-amino-3-(4-hydroxyphenyl)-1-oxopropyl]amino]butyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

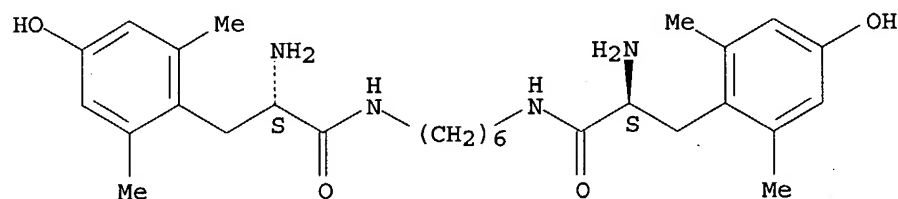


● 2 HCl

RN 573703-36-3 HCAPLUS

CN Benzenepropanamide, N,N'-1,6-hexanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S, α 'S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

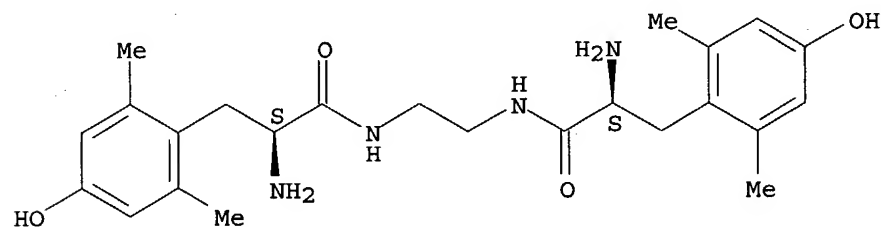


● 2 HCl

RN 649757-28-8 HCAPLUS

CN Benzenepropanamide, N,N'-1,2-ethanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S, α 'S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.

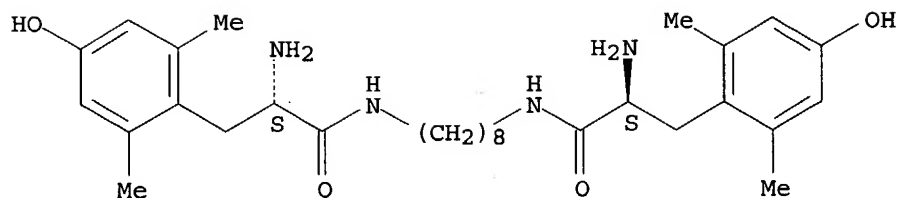


● 2 HCl

RN 649757-31-3 HCAPLUS

CN Benzenepropanamide, N,N'-1,8-octanediylbis[α -amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (α S, α 'S)-(9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

IT 573703-27-2P

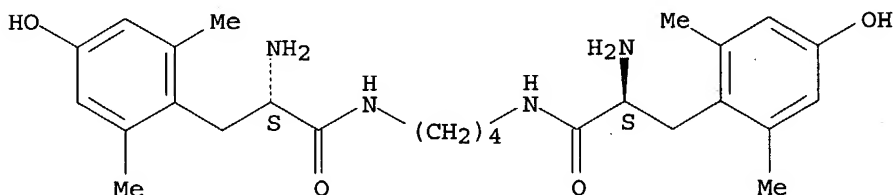
RL: BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(preparation of opioid-mimetics by dimerization of dimethyltyrosine, their conformation, analgesic and opioid receptor-binding structure-activity relationship)

RN 573703-27-2 HCAPLUS

CN Benzenepropanamide, N,N'-1,4-butanediylbis[α-amino-4-hydroxy-2,6-dimethyl-, dihydrochloride, (αS,α'S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



● 2 HCl

L34 ANSWER 4 OF 4 HCAPLUS COPYRIGHT 2004 ACS on STN

AN 1994:534808 HCAPLUS

DN 121:134808

ED Entered STN: 17 Sep 1994

TI preparation of tyrosyl diamide derivatives as analgesics.

IN Hansen, Jr Donald W.; Chandrakumar, Nizal S.; Peterson, Karen B.; Tsymbalov, Sofya; Husa, Robert K.

PA G. D. Searle and Co., USA

SO U.S., 35 pp.

CODEN: USXXAM

DT Patent

LA English

IC ICM A61K031-165

ICS A61K031-325; A61K031-17; C07C237-28

NCL 514487000

CC 34-3 (Amino Acids, Peptides, and Proteins)

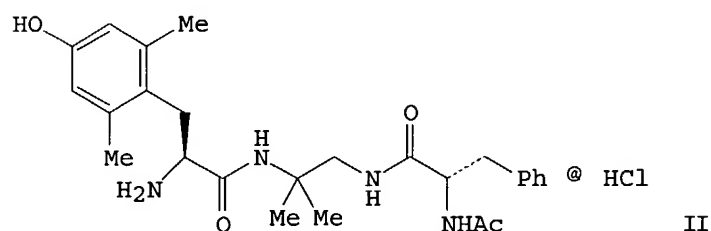
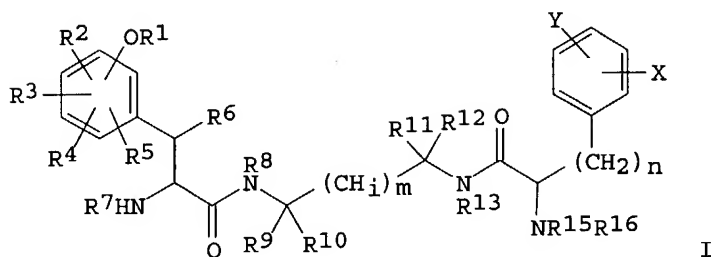
Section cross-reference(s): 1

FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5272175	A	19931221	US 1992-886276	19920520
	US 5364850	A	19941115	US 1993-125897	19930924

PRAI US 1992-886276
OS MARPAT 121:134808
GI

19920520



AB Title compds. [I; R1 = H, alkyl, Ac; R2-R6, R14, R15 = H, alkyl; R7 = H, Me3CO2C; R8-R13 = H, alkyl; R16 = H, Ac, COCF3, etc.; X = H, halo, alkyl; Y = H, alkyl; i = 0-2; m, n = 0-6; and cyclic forms thereof], were prepared. Thus, tert-butoxycarbonyl-L-2,6-dimethyltyrosine and N-acetylphenylalanyl-NHCHCMe2NH2 were stirred with hydroxybenzotriazole and DCC in CH2Cl2 at 0°-room temperature overnight; the resulting coupling product was treated with 7 N HCl in dioxane to give title compound II. II was 7 times more active than the Jacobson compound in the mouse writhing assay, and showed μ and δ opiate receptor binding IC50 values of 0.4 and 0.3 nM, resp.

ST tyrosyl diamide prepn analgesic; peptide analog tyrosyl diamide analgesic
IT Peptides, preparation

RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of tyrosyl diamide derivs. as analgesics)

IT Analgesics
(tyrosyl diamide derivs.)

IT 7764-95-6P, BOC-D-Ala-OH
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

IT	156892-50-1P	156892-51-2P	156892-52-3P	156892-53-4P	156892-54-5P
	156892-55-6P	156892-56-7P	156892-57-8P	156892-58-9P	
	156892-59-0P	156892-60-3P	156892-61-4P	156892-62-5P	156892-63-6P
	156892-64-7P	156892-65-8P	156892-66-9P	156892-67-0P	
	156892-68-1P	156892-69-2P	156892-70-5P	156892-71-6P	156892-72-7P
	156892-73-8P	156892-74-9P	156892-75-0P	156892-76-1P	156892-77-2P
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	156893-03-7P	156893-04-8P	156893-06-0P	156893-07-1P	156893-09-3P
	156893-10-6P	156893-13-9P	156893-14-0P	156893-15-1P	156893-16-2P
	156893-17-3P	156893-18-4P	156893-19-5P	156893-20-8P	156893-21-9P
	156893-22-0P	156893-23-1P	156893-24-2P	156893-25-3P	
	156893-26-4P	156893-27-5P	156893-28-6P	156893-29-7P	156893-30-0P
	156893-31-1P	156893-32-2P	156893-33-3P	156893-34-4P	156893-35-5P

156893-36-6P 156893-37-7P 156893-38-8P 156893-39-9P 156893-42-4P
156893-43-5P 157006-64-9P

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation of, as analgesic)

IT 92502-12-0P 99953-00-1P 100927-10-4P 126312-80-9P 140866-04-2P
145235-85-4P 156892-82-9P 156892-83-0P 156892-84-1P 156892-85-2P
156892-86-3P 156892-87-4P 156892-88-5P 156892-89-6P 156892-90-9P
156892-91-0P 156893-05-9P 156893-08-2P 156893-11-7P 156893-12-8P
156893-40-2P 156893-41-3P

RL: SPN (Synthetic preparation); PREP (Preparation)

(preparation of, as intermediate for analgesic)

IT 99-09-2, m-Nitroaniline 107-15-3, 1,2-Ethanediamine, reactions
330-81-4 407-25-0, Trifluoroacetic anhydride 624-83-9, Methyl
isocyanate 811-93-8, 1,2-Diamino-2-methylpropane 1161-13-3, Z-Phe-OH
1476-23-9, Allyl isocyanate 2018-61-3 2759-28-6 2949-22-6, Ethyl
isocyanatoacetate 3173-56-6, Benzyl isocyanate 3978-80-1, BOC-Tyr-OH
17543-58-7 18471-40-4, 1-Benzyl-3-aminopyrrolidine 35356-70-8, Methyl
2-acetamidoacrylate 42429-20-9 96613-91-1 97268-59-2 99953-00-1
120687-57-2 145235-84-3

RL: RCT (Reactant); RACT (Reactant or reagent)

(reaction of, in preparation of tyrosyl diamide analgesic)

IT 156892-58-9P 156892-66-9P 156893-23-1P
156893-25-3P

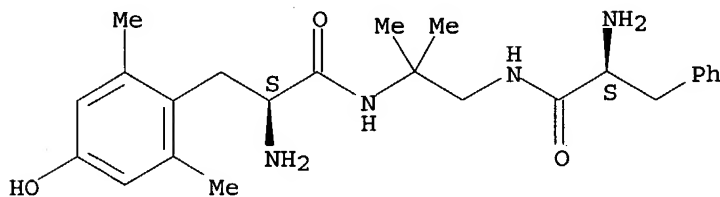
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)

(preparation of, as analgesic)

RN 156892-58-9 HCAPLUS

CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

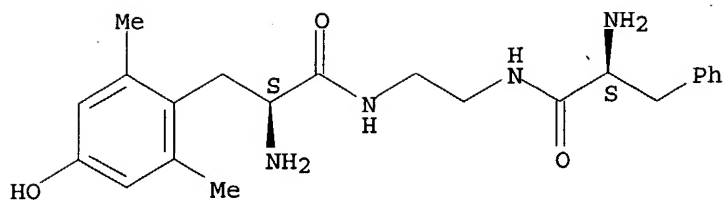


● 2 HCl

RN 156892-66-9 HCAPLUS

CN Benzenepropanamide, α -amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, dihydrochloride, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

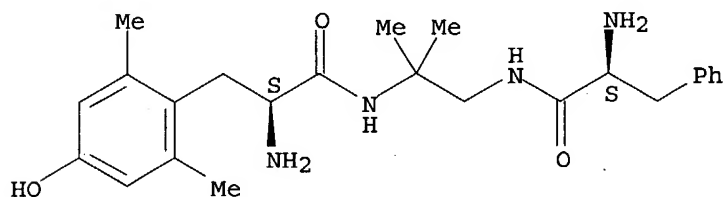


● 2 HCl

RN 156893-23-1 HCAPLUS

CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]-1,1-dimethylethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

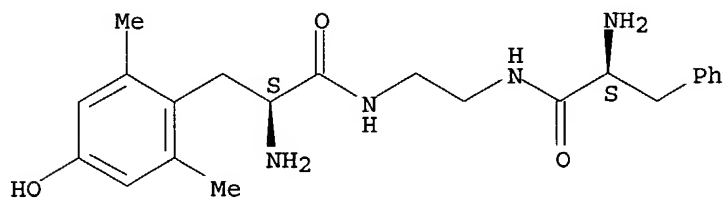
Absolute stereochemistry.



RN 156893-25-3 HCAPLUS

CN Benzenepropanamide, α-amino-N-[2-[(2-amino-1-oxo-3-phenylpropyl)amino]ethyl]-4-hydroxy-2,6-dimethyl-, [S-(R*,R*)]- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



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